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| FORM PTO-1449<br>INFORMATION DISCLOSURE STATEMENT | ATTY. DOCKET NO.<br>0609.4350001/REF/KKV | APPLICATION NO.<br>09/380,704 |
|   | APPLICANT<br>BUSH <i>et al.</i>          |                               |
|   | FILING DATE<br>September 8, 1999         | GROUP<br>To be assigned 1647  |

## U.S. PATENT DOCUMENTS

| EXAMINER INITIAL |     | DOCUMENT NUMBER | DATE       | NAME                  | CLASS | SUB-CLASS | FILING DATE |
|------------------|-----|-----------------|------------|-----------------------|-------|-----------|-------------|
| BEB              | AA1 | 5,242,932       | 09/07/1993 | Gandy <i>et al.</i>   | 514   | 313       | 12/17/1991  |
|                  | AB1 | 5,373,021       | 12/13/1994 | Marangos              | 514   | 483       | 04/26/1993  |
|                  | AC1 | 5,523,295       | 06/04/1996 | Fasman                | 514   | 63        | 07/06/1994  |
|                  | AD1 | 5,688,516       | 11/18/1997 | Raad <i>et al.</i>    | 424   | 409       | 10/03/1994  |
|                  | AE1 | 5,688,651       | 11/18/1997 | Solomon               | 435   | 7.1       | 12/16/1994  |
|                  | AF1 | 5,705,401       | 01/06/1998 | Masters <i>et al.</i> | 436   | 518       | 09/16/1994  |
|                  | AG1 | 5,707,821       | 01/13/1998 | Rydel <i>et al.</i>   | 435   | 18        | 06/07/1995  |
| BEB              | AH1 | 5,721,106       | 02/24/1998 | Maggio <i>et al.</i>  | 435   | 7.8       | 09/12/1994  |

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| EXAMINER INITIAL |     | DOCUMENT NUMBER | DATE       | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
|------------------|-----|-----------------|------------|---------|-------|-----------|-------------|
| BEB              | A11 | WO 92/18111     | 10/29/1992 | WIPO    |       |           | Yes<br>No   |
| BEB              | AJ1 | WO 93/10459     | 05/27/1993 | WIPO    |       |           | Yes<br>No   |
| BEB              | AK1 | WO 93/24451     | 12/09/1993 | WIPO    |       |           | Yes<br>No   |

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| BEB | AL | 1 | Assaf, S.Y and Chung, S.-H., "Release of endogenous Zn <sup>2+</sup> from brain tissue during activity," <i>Nature</i> 308:734-736 (April 1984).   |
|     | AM | 1 | Atwood, C.S. <i>et al.</i> , "Dramatic Aggregation of Alzheimer AB by Cu(II) Is Induced by Conditions Representing Physiological Acidosis," <i>J. Biol. Chem.</i> 273:12817-12826 (May 1998).      |
|     | AN | 1 | Bacon, P.A. <i>et al.</i> , "Rheumatoid Disease, Amyloidosis and its Treatment with Penicillamine," <i>Eur. J. Rheum. Inflamm.</i> 2:70-74 (1979)  |
|     | AO | 1 | Barrow, C.J., and Zagorski, M.G., "Solution Structures of $\beta$ Peptide and Its Constituent Fragments: Relation to Amyloid Deposition," <i>Science</i> 253:179-182 (July 1991).                  |
| BEB | AP | 1 | Barrow, C.J., <i>et al.</i> , "Solution Conformations and Aggregational Properties of Synthetic Amyloid $\beta$ -Peptides of Alzheimer's Disease," <i>J. Mol. Biol.</i> 225:1075-1093 (June 1992). |

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| EXAMINER INITIAL         |     | DOCUMENT NUMBER | DATE       | COUNTRY | CLASS | SUB-CLASS | TRANSLATION   |
| BBB                      | A12 | WO 94/04167     | 03/03/1994 | WIPO    |       |           | <input type="checkbox"/> Yes<br><input type="checkbox"/> No |
| BBB                      | AJ2 | WO 95/31199     | 11/23/1995 | WIPO    |       |           | <input type="checkbox"/> Yes<br><input type="checkbox"/> No |
| BBB                      | AK2 | WO 96/07096     | 03/07/1996 | WIPO    |       |           | <input type="checkbox"/> Yes<br><input type="checkbox"/> No |

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| BBB  | AL | 2 | Basun, H., et al., "Metals and trace elements in plasma and cerebrospinal fluid in normal ageing and Alzheimer's disease," <i>J. Neurol. Transm. [P-D Sect.]</i> 3:231-258 (1991).                      |  |
|  | AM | 2 | Behl, C., et al., "Hydrogen Peroxide Mediates Amyloid $\beta$ Protein Toxicity," <i>Cell</i> 77:817-827 (June 1994).  |  |
|  | AN | 2 | Biaglow, J.E. and Kachur, A.V., "The Generation of Hydroxyl Radicals in the Reaction of Molecular Oxygen with Polyphosphate Complexes of Ferrous Ion," <i>Radiation Res.</i> 148:181-187 (August 1997). |  |
|  | AO | 2 | Boado, R.J. et al., "Drug Delivery of Antisense Molecules to the Brain for Treatment of Alzheimer's Disease and Cerebral AIDS," <i>J. Pharm. Sci.</i> 87(11):1308-1315 (November 1998).                 |  |
| BBB  | AP | 2 | Borman, S., "Diverse Strategies Emerge For Diagnosing Alzheimer's Disease," <i>Chem. Eng. News</i> 272:33-34 (June 1996).   |  |

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|---------------------|-----|-----------------|------------|---------|-------|-----------|-------------|
| beb                 | A13 | WO 96/12544     | 05/02/1996 | WIPO    |       |           | Yes<br>No   |
| beb                 | AJ3 | WO 96/28471     | 09/19/1996 | WIPO    |       |           | Yes<br>No   |
| beb                 | AK3 | WO 97/04794     | 02/13/1997 | WIPO    |       |           | Yes<br>No   |

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|     | AM | 3 | Burdick, D., <i>et al.</i> , "Assembly and Aggregation Properties of Synthetic Alzheimer's A4/B Amyloid Peptide Analogs," <i>J. Biol. Chem.</i> 267:546-554 (January 1992).   |
|     | AN | 3 | Burns, J.A., <i>et al.</i> , "Selective Reduction of Disulfides by Tris(2-carboxyethyl)phosphine," <i>J. Org. Chem.</i> 56:2648-2650 (April 1991).  |
|     | AO | 3 | Busciglio, J., and Yankner, B.A., "Apoptosis and increased generation of reactive oxygen species in Down's Syndrome neurons <i>in vitro</i> ," <i>Nature</i> 378:776-779 (December 1995).                             |
| beb | AP | 3 | Bush, A.I., <i>et al.</i> , "A Novel Zinc(II) Binding Site Modulates the Function of the BA4 Amyloid Protein Precursor of Alzheimer's Disease," <i>J. Biol. Chem.</i> 268:16109-16112 (August 1993).                  |

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|---------------------|-----|-----------------|------------|---------|-------|-----------|-------------|
| BBB                 | AI4 | WO 97/09976     | 03/20/1997 | WIPO    |       |           | Yes<br>No   |
| BBB                 | AJ4 | WO 97/36885     | 10/09/1997 | WIPO    |       |           | Yes<br>No   |
| BBB                 | AK4 | WO 98/06403     | 02/19/1998 | WIPO    |       |           | Yes<br>No   |

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|     | AM | 4 | Bush, A.I., et al., "The Amyloid $\beta$ -Protein Precursor and Its Mammalian Homologues," <i>J. Biol. Chem.</i> 269:26618-26621 (October 1994).  |
|     | AN | 4 | Bush, A.I., et al., "Rapid Induction of Alzheimer A $\beta$ Amyloid Formation by Zinc," <i>Science</i> 265:1464-1467 (September 1994).  |
|     | AO | 4 | Bush, A.I., et al., Response to "Zinc and Alzheimer's Disease," <i>Science</i> 268:1920-1923 (June 1995).   |
| BBB | AP | 4 | Butterfield, D.A., et al., " $\beta$ -Amyloid Peptide Free Radical Fragments Initiate Synaptosomal Lipoperoxidation in a Sequence-Specific Fashion: Implications to Alzheimer's Disease," <i>Biochem. Biophys. Res. Commun.</i> 200:710-715 (April 1994). |

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| BOB                      | AIS | WO 98/40071     | 09/17/1998 | WIPO    |       |           | Yes<br>No   |
| BOB                      | AJS | WO 99/09981     | 03/04/1999 | WIPO    |       |           | Yes<br>No   |
|                          | AK  |                 |            |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |   |  |
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| BOB  | AL | 5 | Butterfield, D.A., et al., "AB(25-35) Peptide Displays H <sub>2</sub> O <sub>2</sub> -Like Reactivity Towards Aqueous Fe <sup>2+</sup> , Nitroxide Spin Probes, and Synaptosomal Membrane Proteins," <i>Life Sci.</i> 58:217-228 (1996). |
|  | AM | 5 | Cherny, R.A. et al., "The Aggregation of AB in Human Brain is Mediated by Zinc," <i>Soc. for Neurosci. Abstracts</i> 23:534 (October 1997).  |
|  | AN | 5 | Chong, Y.-H., and Suh, Y.-H., "Aggregation of amyloid precursor proteins by aluminum in vitro," <i>Brain Research</i> 679:137-141 (January 1995).  |
|  | AO | 5 | Colaco, C.A.L.S., et al., "The role of the Maillard reaction in other pathologies: Alzheimer's disease," <i>Nephrol. Dial. Transplant.</i> 11(Suppl. 5):7-12 (1996).   |
| BOB  | AP | 5 | Connor, J.R. et al., "A Histochemical Study of Iron, Transferrin, and Ferritin in Alzheimer's Diseased Brains," <i>J. Neurosci. Res.</i> 31:75-83 (January 1992).  |

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|                     | AI |                 |      |         |       |           | Yes<br>No   |
|                     | AJ |                 |      |         |       |           | Yes<br>No   |
|                     | AK |                 |      |         |       |           | Yes<br>No   |

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| BEB | AL | 6 | Connor, J.R. et al., "Ceruloplasmin levels in the human superior temporal gyrus in aging and Alzheimer's disease," <i>Neurosci. Lett.</i> 159:88-90 (September 1993).                           |
|     | AM | 6 | Coyle, J.T., and Puttfarcken, P., "Oxidative Stress, Glutamate, and Neurodegenerative Disorders," <i>Science</i> 262:689-695 (October 1993).  |
|     | AN | 6 | Crapper McLachlan, D.R. et al., "Intramuscular desferrioxamine in patients with Alzheimer's disease," <i>Lancet</i> 337:1304-1308 (June 1991).  |
|     | AO | 6 | Cuajungco, M.P. and Lees, G.J., "Zinc and Alzheimer's disease: is there a direct link?" <i>Brain Res. Rev.</i> 23:219-236 (April 1997).   |
| BEB | AP | 6 | Dedman, D.J. et al., "Iron and aluminum in relation to brain ferritin in normal individuals and Alzheimer's-disease and chronic renal-dialysis patients," <i>Biochem J.</i> 287:509-514 (1992). |

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|                     | AJ |                 |      |         |       |           | Yes<br>No   |
|                     | AK |                 |      |         |       |           | Yes<br>No   |

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| BOB | AL | Z | Deibel, M.A. <i>et al.</i> , "Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease: possible relation to oxidative stress," <i>J. Neurol. Sci.</i> 143:137-142 (November 1996).   |
|     | AM | Z | Doré, S., <i>et al.</i> , "Insulin-like growth factor I protects and rescues hippocampal neurons against $\beta$ -amyloid- and human amylin-induced toxicity," <i>Proc. Natl. Acad. Sci. USA</i> 94:4772-4777 (April 1997). |
|     | AN | Z | Dryks, T. <i>et al.</i> , "Amyloidogenicity of $\beta$ A4 and $\beta$ A4-bearing Amyloid Protein Precursor Fragments by Metal-catalyzed Oxidation," <i>J. Biol. Chem.</i> 267:18210-18217 (September 1992).                 |
|     | AO | Z | Ehmann W.D. <i>et al.</i> , "Brain Trace Elements in Alzheimer's Disease," <i>Neurotoxicology</i> 7:197-206 (1986).   |
| BOB | AP | Z | Esler, W.P., <i>et al.</i> , "Zinc-Induced Aggregation of Human and Rat $\beta$ -Amyloid Peptides In Vitro," <i>J. Neurochem.</i> 66:723-732 (February 1996).   |

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|                     | AK |                 |      |         |       |           | Yes<br>No   |

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|     | AM | 8 | Fitzgerald, D.J., "Zinc and Alzheimer's Disease," <i>Science</i> 268:1920 (June 1995).   |
|     | AN | 8 | Folstein, M. "Nutrition and Alzheimer's Disease," <i>Nutrition Reviews</i> 55:23-25 (January 1997).  |
|     | AO | 8 | Fraser, P.E., <i>et al.</i> , "pH-dependent structural transitions of Alzheimer amyloid peptides," <i>Biophys. J.</i> 60:1190-1201 (November 1991).  |
| BEB | AP | 8 | Frederikse, P.H., <i>et al.</i> , "Oxidative Stress Increases Production of $\beta$ -Amyloid Precursor Protein and $\beta$ -Amyloid (A $\beta$ ) in Mammalian Lenses, and A $\beta$ Has Toxic Effects on Lens Epithelial Cells," <i>J. Biol. Chem.</i> 271:10169-10174 (April 1996). |

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| FORM PTO-1449<br>INFORMATION DISCLOSURE STATEMENT  |    |                 |  | ATTY. DOCKET NO.<br>0609.4350001/REF/KKV |                            | APPLICATION NO.<br>09/380,704 |             |
|  |    |                 |  | APPLICANT<br>BUSH <i>et al.</i>          |                            |                               |             |
|  |    |                 |  | FILING DATE<br>September 8, 1999         |                            | GROUP<br>To be assigned 1447  |             |
| U.S. PATENT DOCUMENTS  |    |                 |  |  |                            |                               |             |
| EXAMINER<br>INITIAL  |    | DOCUMENT NUMBER | DATE   | NAME                                     | CLASS                      | SUB-CLASS                     | FILING DATE |
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| FOREIGN PATENT DOCUMENTS   |    |                 |  |  |                            |                               |             |
| EXAMINER<br>INITIAL  |    | DOCUMENT NUMBER | DATE   | COUNTRY                                  | CLASS                      | SUB-CLASS                     | TRANSLATION |
|  | AI |                 |  |  |                            |                               | Yes<br>No   |
|  | AJ |                 |  |  |                            |                               | Yes<br>No   |
|  | AK |                 |  |  |                            |                               | Yes<br>No   |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.)   |    |                 |  |  |                            |                               |             |
| beb  | AL | 2               | Frederickson, C.J., "Neurobiology of Zinc and Zinc-Containing Neurons," <i>Int. Rev. Neurobiol.</i> 31:145-238 (1989).   |  |                            |                               |             |
|  | AM | 2               | Frieden, E., "Ceruloplasmin: A Multi-functional Cupro-protein of Vertebrate Plasma," in: <i>Inflammatory Diseases and Copper</i> , Sorenson, J.R.J., ed., Clifton, N.J.: Humana Press, pp.159-169 (1982).              |  |                            |                               |             |
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| EXAMINER<br><i>Bridget E. Bunner</i>   |    |                 |  |  | DATE CONSIDERED<br>11/4/03 |                               |             |
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ATTY. DOCKET NO.  
0609.4350001/REF/KKV

APPLICATION NO.  
09/380,704

APPLICANT  
BUSH *et al.*

FILING DATE  
September 8, 1999

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To be assigned 1647

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|                     | AI |                 |      |         |       |           | Yes<br>No   |
|                     | AJ |                 |      |         |       |           | Yes<br>No   |
|                     | AK |                 |      |         |       |           | Yes<br>No   |

### OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| FORM PTO-1449<br><b>INFORMATION DISCLOSURE STATEMENT</b>   |    |                 |   | ATTY. DOCKET NO.<br>0609.4350001/REF/KKV |       | APPLICATION NO.<br>09/380,704 |             |
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|  |    |                 |   | FILING DATE<br>September 8, 1999         |       | GROUP<br>To be assigned 1647  |             |
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|  | AI |                 |   |  |       |                               | Yes<br>No   |
|  | AJ |                 |   |  |       |                               | Yes<br>No   |
|  | AK |                 |   |  |       |                               | Yes<br>No   |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.)   |    |                 |   |  |       |                               |             |
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ATTY. DOCKET NO.  
0609.4350001/REF/KKV

APPLICATION NO.  
09/380,704

APPLICANT  
BUSH *et al.*

FILING DATE  
September 8, 1999

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**U.S. PATENT DOCUMENTS**

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|                     | AI |                 |      |         |       |           | Yes<br>No   |
|                     | AJ |                 |      |         |       |           | Yes<br>No   |
|                     | AK |                 |      |         |       |           | Yes<br>No   |

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|  |  |  |  | APPLICANT<br>BUSH et al.                 |  |                               |  |
|  |  |  |  | FILING DATE<br>September 8, 1999         |  | GROUP<br>To be assigned 11647 |  |

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| EXAMINER INITIAL      |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
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| EXAMINER INITIAL         |    | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
|                          | AI |                 |      |         |       |           | Yes<br>No   |
|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |  |
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| FORM PTO-1449<br><br><b>INFORMATION DISCLOSURE STATEMENT</b>   |    |                 |   | ATTY. DOCKET NO.<br>0609.4350001/REF/KKV |                          | APPLICATION NO.<br>09/380,704 |             |
|  |    |                 |   | APPLICANT<br>BUSH <i>et al.</i>          |                          |                               |             |
|  |    |                 |   | FILING DATE<br>September 8, 1999         |                          | GROUP<br>To be assigned 1447  |             |
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| EXAMINER<br>INITIAL  |    | DOCUMENT NUMBER | DATE  | COUNTRY                                  | CLASS                    | SUB-CLASS                     | TRANSLATION |
|  | AI |                 |   |  |                          |                               | Yes<br>No   |
|  | AJ |                 |   |  |                          |                               | Yes<br>No   |
|  | AK |                 |   |  |                          |                               | Yes<br>No   |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.)   |    |                 |   |  |                          |                               |             |
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|  | AJ |                 |   |  |                                |                                     | Yes<br>No   |
|  | AK |                 |   |  |                                |                                     | Yes<br>No   |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.)   |    |                 |   |  |                                |                                     |             |
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|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |
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| FORM PTO-1449<br>INFORMATION DISCLOSURE STATEMENT | ATTY. DOCKET NO.<br>0609.4350001/REF/KKV | APPLICATION NO.<br>09/380,704 |
|   | APPLICANT<br>BUSH <i>et al.</i>          |                               |
|   | FILING DATE<br>September 8, 1999         | GROUP<br>To be assigned 1647  |

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|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |  |  |  |  |  |
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|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

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|   | APPLICANT<br>BUSH et al.                 |                                    |
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|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |           |   |
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APPLICATION NO.  
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APPLICANT  
BUSH *et al.*

FILING DATE  
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|                     | AI |                 |      |         |       |           | Yes<br>No   |
|                     | AJ |                 |      |         |       |           | Yes<br>No   |
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Bridget E. Bunnell

DATE CONSIDERED

11/4/03

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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EXAMINER Bridget E. Dunner

DATE CONSIDERED 11/4/03

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|                          | AI |                 |      |         |       |           | Yes<br>No   |
|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |  |  |  |  |  |
|--|----|----|--|--|--|--|--|
| BOB  | AL | 24 | Roher, A.E., et al., "Morphology and Toxicity of Aβ-(1-42) Dimer Derived from Neuritic and Vascular Amyloid Deposits of Alzheimer's Disease," <i>J. Biol. Chem.</i> 271:20631-20635 (August 1996). |  |  |  |  |
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|   | APPLICANT<br>BUSH et al.                 |                               |
|   | FILING DATE<br>September 8, 1999         | GROUP<br>To be assigned 1647  |

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|                          | AI |                 |      |         |       |           | Yes<br>No   |
|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |  |  |  |  |
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|   | FILING DATE<br>September 8, 1999         | GROUP<br>To be assigned <b>1647</b> |

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| ✓ <i>BEB</i>   | AL | <u>26</u> | Shivers B.D. et al., "Alzheimer's disease amyloidogenic glycoprotein: expression pattern in rat brain suggests a role in cell contact," <i>EMBO J.</i> 7:1365-1370 (1988).                             |  |  |  |  |
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|   | FILING DATE<br>September 8, 1999         | GROUP<br>To be assigned 1647  |

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|                          | AK |                 |      |         |       |           | Yes         |
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |
|--|----|----|---|
| BEB  | AL | 28 | Soto, C., <i>et al.</i> , "Structural Determinants of the Alzheimer's Amyloid $\beta$ -Peptide," <i>J. Neurochem.</i> 63:1191-1198 (October 1994).                              |
|  | AM | 28 | Stankovic, A., and Mitrovic, D.R., "Aluminum Salts Stimulate Luminol-Enhanced Chemiluminescence Production by Human Neutrophils," <i>Free Rad. Res. Comms.</i> 14:47-55 (1991). |
|  | AN | 28 | Tanzi, R.E. <i>et al.</i> , "The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene," <i>Nat. Gen.</i> 5:344-350 (December 1993).     |
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| BEB  | AP | 28 | Tamura, Z., "Clinical Chemistry of Clloquinol," <i>Jpn. J. Med. Sci. Biol.</i> 28:69-77 (1975).   |

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| EXAMINER<br><i>Bridget C. Dunner</i> | DATE CONSIDERED<br>11/4/03 |
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |
|--|----|----|---|
| BEB  | AL | 29 | Tateishi, J. et al., "Strain-differences in dogs for neurotoxicity of clioquinol," <i>Lancet</i> 1:1289-1290 (June 1972).   |
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |  |
|--|----|----|--|
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |
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| Bob  | AL | 31 | Tomiyama, T., <i>et al.</i> , "Inhibition of Amyloid $\beta$ Protein Aggregation and Neurotoxicity by Rifampicin," <i>J. Biol. Chem.</i> 271:6839-6844 (March 1996).                                |
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| FORM PTO-1449<br><br>INFORMATION DISCLOSURE STATEMENT | ATTY. DOCKET NO.<br>0609.4350001/REF/KKV | APPLICATION NO.<br>09/380,704      |
|   | APPLICANT<br>BUSH <i>et al.</i>          |                                    |
|   | FILING DATE<br>September 8, 1999         | GROUP<br>To be assigned <i>647</i> |
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| U.S. PATENT DOCUMENTS |    |                 |      |      |       |           |             |
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| EXAMINER INITIAL      |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
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|                          | AI |                 |      |         |       |           | Yes         |
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|                          | AJ |                 |      |         |       |           | Yes         |
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|                          | AK |                 |      |         |       |           | Yes         |
|                          |    |                 |      |         |       |           | No          |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |           |   |
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| <i>Bob</i>   | AL | <u>32</u> | Warren, P.J. <i>et al.</i> , "The Distribution of Copper in Human Brain," <i>Brain</i> . 83:709-717 (1960).   |
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| EXAMINER<br><i>Bridget E. Turner</i> | DATE CONSIDERED<br><i>11/4/03</i> |
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| FORM PTO-1449<br>INFORMATION DISCLOSURE STATEMENT | ATTY. DOCKET NO.<br>0609.4350001/REF/KKV | APPLICATION NO.<br>09/380,704 |
|   | APPLICANT<br>BUSH <i>et al.</i>          |                               |
|   | FILING DATE<br>September 8, 1999         | GROUP<br>To be assigned 1647  |

| U.S. PATENT DOCUMENTS |    |                 |      |      |       |           |             |
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| EXAMINER INITIAL      |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
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|                          | AK |                 |      |         |       |           | Yes         |
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |  |  |  |  |
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| /  | AM | 33 | Linert, W. <i>et al.</i> , "Dopamine, 6-hydroxydopamine, iron, and dioxygen-their mutual interaction and possible implication in the development of Parkinson's disease," <i>Biochim. Biophys. Acta</i> 1316:160-168 (August 1996). |  |  |  |  |
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| EXAMINER<br><i>Bridget E. Burner</i>   | DATE CONSIDERED<br>11/4/03 |
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**FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

ATTY. DOCKET NO.  
0609.4350001/REF/KKV

APPLICATION NO.  
09/380,704

APPLICANT  
BUSH et al.

FILING DATE  
September 8, 1999

GROUP  
To be assigned 1647

**U.S. PATENT DOCUMENTS**

| EXAMINER<br>INITIAL |     | DOCUMENT NUMBER | DATE       | NAME                 | CLASS | SUB-CLASS | FILING DATE |
|---------------------|-----|-----------------|------------|----------------------|-------|-----------|-------------|
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|                     | AB  |                 |            |                      |       |           |             |
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**FOREIGN PATENT DOCUMENTS**

| EXAMINER<br>INITIAL |    | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
|---------------------|----|-----------------|------|---------|-------|-----------|-------------|
|                     | AI |                 |      |         |       |           | Yes<br>No   |
|                     | AJ |                 |      |         |       |           | Yes<br>No   |
|                     | AK |                 |      |         |       |           | Yes<br>No   |

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

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|-----|----|----|---|
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|     | AO |    |   |
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EXAMINER Bridget C. Bunner

DATE CONSIDERED 11/4/03

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**FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

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0609.4350001/REF/KKV

APPLICATION NO.  
09/380,704

APPLICANT  
BUSH *et al.*

FILING DATE  
September 8, 1999

GROUP  
To be assigned 1147

**U.S. PATENT DOCUMENTS**

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|                     | AI |                 |      |         |       |           | Yes<br>No   |
|                     | AJ |                 |      |         |       |           | Yes<br>No   |
|                     | AK |                 |      |         |       |           | Yes<br>No   |

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

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| <i>bed</i> | AL | 34 | Schrader-Fischer, G. and P.A. Paganetti, "Effect of alkalizing agents on the processing of the $\beta$ -amyloid precursor protein," <i>Brain Research</i> 716:91-100 (April 1996) |
|            | AM |    |   |
|            | AN |    |   |
|            | AO |    |   |
|            | AP |    |   |

EXAMINER *Bridget C. Bunner*

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| FORM PTO-1449<br><br><b>SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT</b>   |    |                 |  | ATTY. DOCKET NO.<br>0609.4350001 |                                | APPLICATION NO.<br>09/380,704 |             |
|  |    |                 |  | APPLICANT<br>Bush et al.         |                                |                               |             |
|  |    |                 |  | 102 (e) DATE<br>June 6, 2000     |                                | GROUP<br>1636 1647            |             |
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| EXAMINER<br>INITIAL  |    | DOCUMENT NUMBER | DATE   | NAME                             | CLASS                          | SUB-CLASS                     | FILING DATE |
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| FOREIGN PATENT DOCUMENTS   |    |                 |  |                                  |                                |                               |             |
| EXAMINER<br>INITIAL  |    | DOCUMENT NUMBER | DATE   | COUNTRY                          | CLASS                          | SUB-CLASS                     | TRANSLATION |
|  |    |                 |  |                                  |                                |                               | Yes<br>No   |
|  | AI |                 |  |                                  |                                |                               | Yes<br>No   |
|  | AJ |                 |  |                                  |                                |                               | Yes<br>No   |
|  | AK |                 |  |                                  |                                |                               | Yes<br>No   |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.)   |    |                 |  |                                  |                                |                               |             |
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| EXAMINER <i>Bridget E. Bunner</i>  |    |                 |  |                                  | DATE CONSIDERED <i>11/4/03</i> |                               |             |
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| FORM PTO-1449<br><br><b>SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT</b> |  | ATTY. DOCKET NO.<br>0609.4350001 |  | APPLICATION NO.<br>09/380,704 |  |
| APPLICANT<br>Bush et al.   |  | 102 (e) DATE<br>June 6, 2000     |  | GROUP<br>1646 1647            |  |

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|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |
|--|----|----|---|
| BOB  | AL | 35 | Cohen, A.S., "Amyloidosis," <u>Arthritis and Allied Conditions: A Textbook of Rheumatology</u> , D.J. McCarty, ed., Lea and Febiger, Philadelphia, pp. 1273-1293 (1989).  |
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| EXAMINER <u>Bridget E. Bunner</u> | DATE CONSIDERED <u>11/4/03</u> |
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| FORM PTO-1449<br>SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT | ATTY. DOCKET NO.<br>0609.4350001 | APPLICATION NO.<br>09/380,704 |
|   | APPLICANT<br>Bush et al.         |                               |
|   | 102(e) DATE<br>June 6, 2000      | GROUP<br>1616 1647            |

| U.S. PATENT DOCUMENTS |    |                 |      |      |       |           |             |
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| EXAMINER INITIAL      |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
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| EXAMINER INITIAL         |    | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
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|                          | AJ |                 |      |         |       |           | Yes<br>No   |
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| BeB | AL | 36 | Kuo, Y.-M., et al., "High Levels of Circulating Aβ42 Are Sequestered by Plasma Proteins in Alzheimer's Disease," <i>Biochem. Biophys. Res. Commun.</i> 257:787-791 (April 1999).            |
|     | AM | 36 | Lovell, M.A., et al., "Copper, iron and zinc in Alzheimer's disease senile plaques," <i>J. Neurol. Sci.</i> 158:47-52 (June 1998).  |
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| EXAMINER<br>Bridget C. Bunner | DATE CONSIDERED<br>11/4/03 |
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| FORM PTO-1449<br><br><b>SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT</b> |  |  |  | ATTY. DOCKET NO.<br>0609.4350001 |  | APPLICATION NO.<br>09/380,704 |  |
|  |  |  |  | APPLICANT<br>Bush et al.         |  |                               |  |
|  |  |  |  | 102 (e) DATE<br>June 6, 2000     |  | GROUP<br>1647                 |  |

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|                          | AI |                 |      |         |       |           | Yes<br>No   |
|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |
|--|----|----|---|
| <div style="font-size: 2em; font-family: cursive;">BEB</div> | AL | 37 | Pepys, M.B. and Baltz, M.L., "Acute Phase Proteins with Special Reference to C-Reactive Protein and Related Proteins (Pentaxins) and Serum Amyloid A Protein," in <i>Advances in Immunology</i> , Vol. 34, pp.141-212 (1983). |
| <div style="font-size: 2em; font-family: cursive;">/</div>   | AM | 37 | Raby, C.A., et al., "Traumatic Brain Injury Increases $\beta$ -Amyloid Peptide 1-42 in Cerebrospinal Fluid," <i>J. Neurochem.</i> 71:2505-2509 (December 1998).   |
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| EXAMINER <span style="font-size: 1.2em; font-family: cursive;">Bridget C. Burner</span> | DATE CONSIDERED <span style="font-size: 1.2em; font-family: cursive;">11/4/03</span> |
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| FORM PTO-1449<br>SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT | ATTY. DOCKET NO.<br>0609.4350001 | APPLICATION NO.<br>09/380,704 |
|   | APPLICANT<br>Bush et al.         |                               |
|   | 102 (e) DATE<br>June 6, 2000     | GROUP<br>1614 1647            |

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| EXAMINER INITIAL      |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
|                       | AA |                 |      |      |       |           |             |
|                       | AB |                 |      |      |       |           |             |
|                       | AC |                 |      |      |       |           |             |
|                       | AD |                 |      |      |       |           |             |
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|                       | AG |                 |      |      |       |           |             |
|                       | AH |                 |      |      |       |           |             |

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| EXAMINER INITIAL         |    | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
|                          | AI |                 |      |         |       |           | Yes<br>No   |
|                          | AJ |                 |      |         |       |           | Yes<br>No   |
|                          | AK |                 |      |         |       |           | Yes<br>No   |

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| BOB | AL | 38 | Terry, R.D., et al., "Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss is the Major Correlate of Cognitive Impairment," <i>Ann. Neurol.</i> 30:572-580 (October 1991).   |
|     | AM | 38 | Uchida, K. and Kawakishi, S., "Identification of oxidized Histidine Generated at the Active Site of Cu,Zn-Superoxide Dismutase Exposed to H <sub>2</sub> O <sub>2</sub> . Selective Generation Of 2-Oxo-Histidine At The Histidine 118," <i>J. Biol. Chem.</i> 269:2405-2410 (January 1994). |
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| EXAMINER<br>Bridget C. Dunner | DATE CONSIDERED<br>11/4/03 |
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| FORM PTO-1449<br><b>INFORMATION DISCLOSURE STATEMENT</b> |  |  |  | ATTY. DOCKET NO.<br>0609.4350001/JAG/KKV |  | APPLICATION NO.<br>09/380,704 |  |
|  |  |  |  | APPLICANT<br>Bush et al.                 |  |                               |  |
|  |  |  |  | 102(e) Date<br>June 6, 2000              |  | GROUP<br>1647                 |  |

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| EXAMINER INITIAL      |     | DOCUMENT NUMBER | DATE       | NAME               | CLASS | SUB-CLASS | FILING DATE |
|                       | AA2 |                 |            |                    |       |           |             |
|                       | AB2 |                 |            |                    |       |           |             |
| BBB                   | AC2 | 5,110,493       | 05/05/1992 | Cherng-Chyi et al. | 514   | 413       | —           |
| BBB                   | AD2 | 5,466,680       | 11/14/1995 | Rudy               | 514   | 57        | —           |
|                       | AE  |                 |            |                    |       |           |             |
|                       | AF  |                 |            |                    |       |           |             |
|                       | AG  |                 |            |                    |       |           |             |
|                       | AH  |                 |            |                    |       |           |             |
|                       | AI  |                 |            |                    |       |           |             |
|                       | AJ  |                 |            |                    |       |           |             |
|                       | AK  |                 |            |                    |       |           |             |

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| EXAMINER INITIAL         |    | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
|                          | AL |                 |      |         |       |           | Yes<br>No   |
|                          | AM |                 |      |         |       |           | Yes<br>No   |
|                          | AN |                 |      |         |       |           | Yes<br>No   |
|                          | AO |                 |      |         |       |           | Yes<br>No   |
|                          | AP |                 |      |         |       |           | Yes<br>No   |

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| BBB  | AP | 32 | Lodemann, E., Naturwissenschaften 66(9): 462-466 (September 1979) (publisher: Springer-Verlag)                                      |
| BBB  | AL | 40 | Sue, Y.-J. et al., Annals of Emergency Medicine 24(4): 709-712 (October 1994) (publisher: American College of Emergency Physicians) |

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| THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT |  | APPLICANT<br>Bush et al.         |                               |
|   |  | 102 (e) DATE<br>June 6, 2000     | GROUP<br>164 1647             |

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| EXAMINER INITIAL |     | DOCUMENT NUMBER | DATE       | NAME           | CLASS | SUB-CLASS | FILING DATE |
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|                  | AA  |                 |            |                |       |           |             |
| BOB              | AB2 | 5,927,283       | 07/27/1999 | Abraham et al. | 128   | 898       | 05/08/1997  |
|                  | AC  |                 |            |                |       |           |             |
|                  | AD  |                 |            |                |       |           |             |
|                  | AE  |                 |            |                |       |           |             |
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## FOREIGN PATENT DOCUMENTS

| EXAMINER INITIAL |     | DOCUMENT NUMBER | DATE       | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
|------------------|-----|-----------------|------------|---------|-------|-----------|-------------|
|                  | AI  |                 |            |         |       |           | Yes<br>No   |
|                  | AJ  |                 |            |         |       |           | Yes<br>No   |
| BOB              | AK5 | WO 99/18432     | 04/15/1999 | WIPO    |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

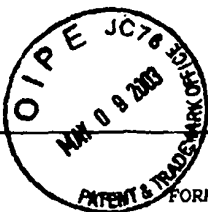
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| BOB | AL | 39 | Atwood, C.S. et al., "Role of Free Radicals and Metal Ions in the Pathogenesis of Alzheimer's Disease," in <i>Metal Ions in Biological Systems</i> , Sigel, A. and Sigel H., eds., Vol. 36, Ch. 10, Marcel Dekker Inc., New York, pp. 309-364 (1999). |
| BOB | AM | 39 | McKeon-O'Mally, C., et al., "Potential Therapeutic Targets for Alzheimer's Disease," <i>Emerging Therapeutic Targets</i> 2:157-179, Ashley Publications Ltd. (1998).  |
|     | AN | 39 | <del>International Search Report for PCT/US00/11715, mailed August 30, 2000.</del>  |
|     | AO |    |   |
|     | AP |    |   |

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| FORM PTO-1449<br><b>SEVENTH SUPPLEMENTAL<br/>INFORMATION DISCLOSURE STATEMENT</b> | ATTY. DOCKET NO.<br>0609.4350001/JAG/FRC | APPLICATION NO.<br>09/380,704 |
|   | APPLICANT<br>BUSH et al.                 |                               |
|   | \$ 102(e) Date:<br>June 6, 2000          | GROUP<br>1647                 |

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| EXAMINER<br>INITIAL   |     | DOCUMENT NUMBER | DATE       | NAME      | CLASS | SUB-CLASS | FILING DATE |
|                       | AA  |                 |            |           |       |           |             |
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|                       | AF  |                 |            |           |       |           |             |
|                       | AG  |                 |            |           |       |           |             |
|                       | AH2 | 4,419,365       | 12/06/1983 | McLachlan |       |           | 12/21/1981  |

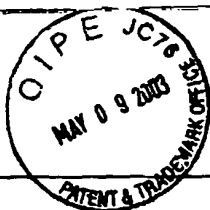
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| BEB                      | AI6 | DE 40 04 978 A1 | 08/22/1991 | Germany | —     | —         | Yes<br>No   |
| BEB                      | AJ6 | WO 94/27594 A2  | 12/08/1994 | WIPO    | —     | —         | Yes<br>No   |
| BEB                      | AK6 | WO 96/39144 A1  | 12/12/1996 | WIPO    | —     | —         | Yes<br>No   |

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|     | AR |    |   |
| BEB | AS | 40 | BIOMOL Product Data for TPEN, Catalog No. AP-300, Lot No. P3707, BIOMOL Research Laboratories, Inc. Plymouth Meeting, PA (July 2002)                                |
| BEB | AT | 40 | Cardelli, M., et al., "Chelation Therapy. Unproved Modality in the Treatment of Alzheimer-Type Dementia," J. Am. Geriatr. Soc. 33:548-551, Blackwell Science (1985) |

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|   | APPLICANT<br>BUSH et al.                 |                               |
|   | \$ 102(e) Date:<br>June 6, 2000          | GROUP<br>1647                 |

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| BBB                 | AA3 | 5,310,936       | 05/10/1994 | Regtop et al. |       |           | 01/15/1992  |
|                     | AB  |                 |            |               |       |           |             |
|                     | AC  |                 |            |               |       |           |             |
|                     | AD  |                 |            |               |       |           |             |
|                     | AE  |                 |            |               |       |           |             |
|                     | AF  |                 |            |               |       |           |             |
|                     | AG  |                 |            |               |       |           |             |
|                     | AH  |                 |            |               |       |           |             |

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|---------------------|-----|-----------------|------------|---------|-------|-----------|-------------|
| BBB                 | AI7 | WO 97/01559 A1  | 01/16/1997 | WIPO    |       |           | Yes<br>No   |
|                     | AJ  |                 |            |         |       |           | Yes<br>No   |
|                     | AK  |                 |            |         |       |           | Yes<br>No   |

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|   | \$ 102(e) Date:<br>June 6, 2000          | GROUP<br>1647                 |

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|                     | AA |                 |      |      |       |           |             |
|                     | AB |                 |      |      |       |           |             |
|                     | AC |                 |      |      |       |           |             |
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|                     | AI |                 |      |         |       |           | Yes<br>No   |
|                     | AJ |                 |      |         |       |           | Yes<br>No   |
|                     | AK |                 |      |         |       |           | Yes<br>No   |

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| <i>Bob</i> | AR | 42 | Van Reyk, D.M., and Dean, R.T., "The Iron-selective Chelator Desferal Can Reduce Chelated Copper," <i>Free Radic. Res.</i> 24:55-60, Harwood Academic Publishers GmbH (January 1996) |
|            | AS | 42 | <del>Diales File 351, Accession No. 8749401, Derwent WPI English language abstract for DE 4004978.</del>   |
|            | AT |    |  |

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